Unique and Efficient Synthesis of [2*S*-(2*R**,3*S**,4*R**)]-2-Amino-1-cyclohexyl-6-methyl-3,4-heptanediol, a Popular C-Terminal Component of Many Renin Inhibitors

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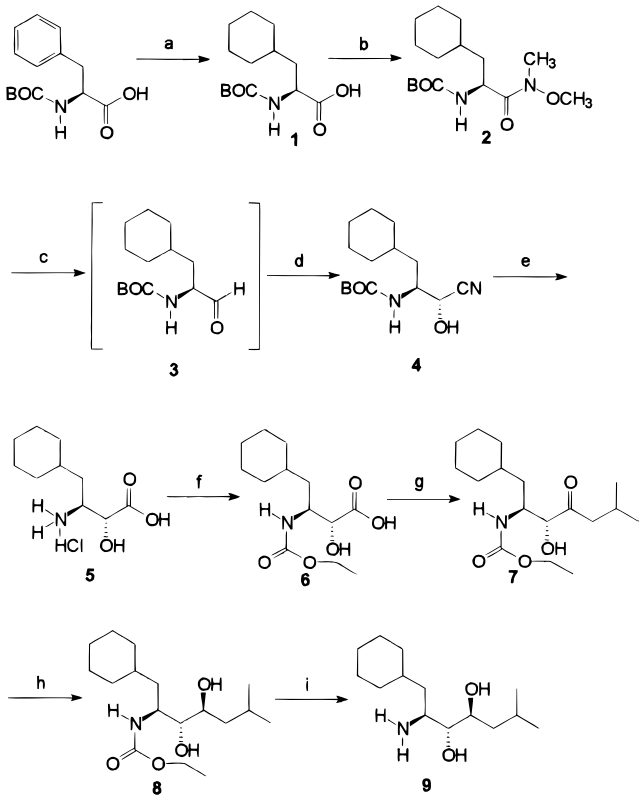
Introduction

Many compounds containing 1-amino-2,3-diol functionalities have antihypertensive activity and act as renin inhibitors.[1] Aminodiols have also been reported to have other biological properties such as a gastro protective substance[2] and inhibitors of the HIV protease and antiviral activity.[3] On a broader scope, a number of amino sugars and polyhydroxylated alkaloids have been reported to be useful in the treatment of carbohydrate dependant metabolic disorders due to their selective inhibition of glycosidases.[4] New synthetic routes to amino alcohols would be useful in the synthesis of compounds in all these areas.

Our interest in 1-amino-2,3-diols was in the economical synthesis of [2*S*-(2*R**,3*S**,4*R**)]-2-amino-1-cyclohexyl-6-methyl-3,4-heptanediol (**9**), PD 134373—a segment of CI-992—a compound Parke-Davis intended for the treatment of hypertension and congestive heart failure.[5] The original preparation of **9** was a multistep low-yielding synthesis starting from L-phenylalanine utilizing an OsO_4 oxidation of a *cis*-alkene.[6] Many research groups have sought to overcome the problems associated with the osmylation oxidation procedure.[7]

Scheme 1[a]



[a] (a) H_2, 2% Rh−10% Pd/C; (b) $ClCO_2Et$, MeHNOMe, HCl; (c) LAH; (d) acetone cyanohydrin, catalytic KCN, TBAI; (e) HCl; (f) NaOH, $ClCO_2Et$; (g) iBuLi, THF/LiBr; (h) $NaB(O_2CCH_3)_3H$; (i) KOH.

Our unique and improved synthesis involved the linear addition of two inexpensive low molecular weight fragments in a stereochemically controlled manner illustrated in Scheme 1. Relative chirality was controlled by the isolation of cyanohydrin **4** and subsequent reduction of **7** to **8**. The key synthetic strategy surrounds the lithium carboxylate of **6** coupling with isobutyllithium. This route converted BOC-phenylalanine (BOC-Phe) to the aminodiol **9** in eight steps on a multikilogram scale (overall yield of 37%). The elegance of the synthetic route was the combination of steps with the right chemistry that was reliably prepared on a large scale. The overall yield and stereoselectivity of this new synthesis were better than those of previously described routes.

Results and Discussion

The key aspects of this new synthesis are (1) direct isolation of a single diastereomer of cyanohydrin **4**, (2) unique conversion of the acid **5** to the β-amino α-hydroxy ketone **7**, and (3) improved selective reduction of the ketone **7** to the desired aminodiol diastereomer **8**. The majority of the discussion entails details for these key steps.

The synthetic process begins with the reduction of BOC-Phe to the cyclohexyl analogue **1** by standard methods.[8] In the second step the preferred method of reduction from the amino acid **1** to aldehyde **3** was via the methoxymethylamide **2**. Aldehyde **3** underwent

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reaction with cyanide resulting in a mixture of diastereomeric isomers including cyanohydrin **4**.

The mixture of cyanohydrins was purified and isolated by crystallization to the desired diastereomer in good yield, an advantage over published alternatives.[9] These other methods do not isolate a single diastereomer but carry the mixture on through the acid hydrolysis to obtain crystalline **5** in about 60% yields.[9] Both classical bisulfite and acetone cyanohydrin methods work equally well on a laboratory scale to prepare crude cyanohydrin **4**. The new methodology in the preparation of **4** is the isolation of the desired pure crystalline diastereomer out of a hydrocarbon and water solvent mixture. Crystallization from a two-phase mixture of hexane or heptane and water gave **4** in 65−90% isolated yields. This new procedure reliably allowed up to a 90% isolated yield of solid **4** on a laboratory scale.

The desired cyanohydrin diastereomer **4** seemed to be produced with very high selectivity, but significant epimerization was found to occur over time in solution. A solid isolation of this compound was desirable due to the nature of the cyanohydrin to epimerize in solution. On a laboratory scale the isolation of **4** works very well. Isolation of **4** by crystallization was aimed to minimize epimerization on a large scale reaction.[10]

An epimerization study using a HPLC solution containing pure cyanohydrin **4** illustrated that the single cyanohydrin diastereomer was stable in solution until a catalytic amount of potassium cyanide (KCN) was added. Upon addition of KCN, the cyanohydrin epimerized over time to a 1:1 mixture of diastereomers. Epimerization was also verified in an NMR study comparing ^{13}C NMR spectra, before and after KCN addition. Without the isolation of the solid **4**, a reliable assay of the crude diastereomeric mixture content was difficult to obtain.

In our case the conversion of cyanohydrin **4** to β-amino α-hydroxy acid **5** also used acid conditions.[9] Use of the isolated solid **4** allowed conversion in up to 98% yield to the acid **5**. The workup procedures of **5** were much easier using the solid **4** than with the diastereomeric oily crude mixtures of **4**.

The most complex and intriguing step was the lithium carboxylate of **6** coupling with isobutyllithium to prepare ketone **7**. The addition of organometallic reagents to carboxylic acid derivatives is known,[11] yet several problems have limited the use of these reactions. The major concerns are that organometallic reagents are basic as well as nucleophilic, resulting in deprotonation rather than addition and the double addition of the organometallic reagent to the ketone to produce a tertiary alcohol. Several research groups have recently introduced methods to overcome these problems.[12] Still, examples of good yielding ketone formation reactions involving an unprotected heteroatom or "multianionic intermediate" species are limited and plagued with problems. Insolubility and aggregation of lithium species have been thought to contribute to the low yields in these reactions. The complexities of working with multianionic metal species in solution have been the subject of a recent paper.[13] We were able to overcome all of these problems. The best procedure for preparing the ketone **7** involved the following parameters: toluene/heptane solvents, controlled low temperature to minimize impurities, and the presence of lithium bromide (LiBr)/tetrahydrofuran (THF) to modify lithium aggregates. The addition of LiBr/THF was a key factor that allowed us to prepare the β-amino α-hydroxy ketone **7** from **6** in good yields.

An experimental design study was initially used to determine the most important processing parameters of the coupling reaction to **7**. Crude HPLC yields were used as the measure of response (data analyzed by Design-Ease software). The experimental design study gave us a broad overview of the reaction parameters. The design results quickly gave us an idea of which parameters were interactive and to what the consequences of these interactions would lead. The design indicated interactions between (a) addition time and concentration, (b) addition time and addition temperature, and (c) addition temperature and reaction temperature. The three important findings from the statistical study are summarized as follows: (1) There was a high probability that product purity increased with more equivalents of isobutyllithium, the higher concentration of starting material, and increased reaction temperature, (2) the addition temperature seemed to have the lowest probability of having any effect on the product purity, and (3) the reaction temperature parameter appeared to favor the higher temperatures. Because of the interactive parameters, prior to the experimental design, it appeared that a change in conditions resulted in wildly random yields. We could now focus on the important parameter conditions and avoid those that resulted in drastically lower yields. The biggest problem was getting the reaction to go to completion. In all conditions investigated, the starting material **6** remained as the main impurity. The major contributor to this problem was thought to be solvation of various intermediates.

Various solvent systems were explored after it became clear that the reaction conditions studied would not produce a complete reaction. An apparent multianionic lithium salt intermediate precipitated during the iBuLi addition with the THF/heptane system. Very thick slurries were produced in the 0.3−0.5 M reaction mixtures at <-10 °C using toluene. No precipitation was observed in reactions using methyl-*tert*-butyl ether (MTBE) under similar conditions, an improvement over toluene. Toluene gave the better yields, but as with all solvent systems attempted, the starting material was still the major impurity in the product.

The work with different solvents suggested product/impurity ratios were influenced by solvent, but a satisfactory ratio was not achieved. It was noted that the reaction worked best in an ethereal solvent (diethyl ether, THF, or MTBE). The literature suggests that lithium aggregates may be possible and could be modified or broken up with additives such as lithium chloride (LiCl)

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(10) The longer reaction and workup times involved in a large scale reaction were a concern for epimerization. On a 20 kg scale, a 42% yield was obtained for the combined reaction steps preparing **3** and **4**. We believe the lower large scale yield was also due to larger than expected amounts of the corresponding alcohol present arising from overreduced aldehyde **3**. Both of these factors contributed to the lower isolation yield in the crystallization process of **4**. Pursuit in optimizing the scale-up process of this reaction was dropped due to finding a commercial kilogram quantity source for **5** (Nippon Kayaku Co., Ltd.).

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or tetramethylethylenediamine (TMEDA).[13] While incomplete reactions were still observed with the incorporation of the additives LiCl and TMEDA, a dramatic improvement in yield and purity was observed with the addition of LiBr in THF. A strong exotherm was observed while dissolving the LiBr in THF, indicating an immediate complexing between the salt and the solvent.[14] The success of using LiBr/THF as an additive demonstrated that the incomplete reactions were likely the result of aggregates.

Our previous work had shown that reaction byproduct impurities were reduced in a toluene solvent. A mixed toluene/THF solvent system was examined after it was found that LiBr could be solubilized by adding only a small amount of THF. The isolated yields, when corrected for purity, resulted in conversions of 80−85% of the starting material **6** to **7**. The modification of lithium aggregates by use of the LiBr/THF combination was critical for the reaction to go to completion. Impurities were minimized by using optimum parameters: addition temperatures (−10 °C), reaction temperatures (10 °C), and equivalents of iBuLi (4.15). High product conversions were achieved with a 2−3 h reaction time under these conditions. The toluene/LiBr/THF system was superior to both the THF/LiBr and the toluene systems. This provided definite proof that addition of small amounts of THF/LiBr was critical and favorably affected the solvation influencing the reaction.

The order of the quench addition influenced the formation of a tertiary alcohol impurity resulting from double addition.[11,12] The tertiary alcohol impurity was minimized by adding the reaction solution to water while rapidly stirring the solution at <10 °C. There was also some indication that the tertiary alcohol impurity was more easily formed in the toluene systems than in ether solvents. This may be the result of reduced solubility in the two-phase quench.

An unknown 1% impurity was observed and traced to **9** made from the method using toluene. It was removed by a recrystallization of the **9** material, isolated from the recrystallization filtrate by chromatography, and identified as a toluene derivative of **9**. This impurity was created by conversion of a small amount of toluene to phenylmethyllithium which competed with isobutyllithium for the carboxylate in the coupling reaction to aminodiol **8**.[15] This could be avoided in the future by use of MTBE or possibly ethylbenzene.

Reduction of the β-amino α-hydroxy ketone **7** to the desired aminodiol **8** was known to occur with good stereoselectivity.[7a] Reduction studies of **7** with different solvents and reagents resulted in significant improvements in the selectivity to the aminodiol **8**. The resulting diastereomeric ratio was found to be dependent upon the reducing reagent and solvent used. A mixture of the two possible reduction diastereomers of **8** was determined from a doubling of peaks observed in both ^{13}C NMR and HPLC data. The ratio of undesired/desired diastereomer was found to be 60/40 using sodium borohydride in methanol, 18/82 using sodium borohydride in THF, and 1/100 using sodium triacetoxyborohydride in both THF and a mixture of heptane and acetonitrile. Sodium triacetoxyborohydride was a superior selective reducing reagent over sodium borohydride or sodium cyanoborohydride in THF resulting in the desired aminodiol **8**.

Deprotection of the amine functionality of the aminodiol **8** to the free amine **9** went as expected. The ethylcarbamate protecting group was hydrolyzed to the amine using potassium hydroxide in excellent yield.

Summary

A new, simple, large scale route to [2*S*-(2*R**,3*S**,4*R**)]-2-amino-1-cyclohexyl-6-methyl-3,4-heptanediol (**9**) was established starting from BOC-Phe. Diastereoselectivity was improved by selective crystallization of pure cyanohydrin diastereomer **4** and using a sodium triacetoxyborohydride reagent in the reduction of β-amino α-hydroxy ketone **7**. Aggregate and solvation problems dealing with multianionic intermediates in the carboxylate coupling to β-amino α-hydroxy ketone **7** were overcome by introducing a toluene/LiBr/THF solvent system. The synthetic route consists of eight steps starting from BOC-Phe and results in a 37% overall yield. All but two steps were run on a multikilogram scale. These two steps preparing **4** and **5** worked excellently on a large (>150 g) laboratory scale.

We have demonstrated a traditional synthetic approach to [2*S*-(2*R**,3*S**,4*R**)]-2-amino-1-cyclohexyl-6-methyl-3,4-heptanediol (**9**) by controlling stereochemistry of each additional chiral center starting from a chiral amino acid, BOC-Phe. This overall efficient and practical synthetic strategy should be applicable to a wide variety of 1-amino-2,3-diols utilizing commercially available chiral amino acids as starting materials and varying the lithium alkyl used in the coupling reaction.

Experimental Section

(*S*)-α-[[(1,1-Dimethylethoxy)carbonyl]amino]cyclohexanepropanoic Acid (1). *N*-(*tert*-Butyloxycarbonyl)-L-phenylalanine (29.9 kg, 112.7 mol) and 1.94 kg of 2% Rh−10% Pd on carbon catalyst was stirred with 300 L of isopropyl alcohol. The reaction mixture was pressurized to 50 psig with hydrogen at about 50 °C until hydrogen consumption ceased. The resulting slurry was cooled to about 15 °C and filtered. The wet catalyst was rinsed with 29 L of isopropyl alcohol. The combined filtrates were concentrated to an oil by vacuum distillation (5−10 mmHg) at 50−55 °C. All residual IPA was removed by addition of 97 L of toluene followed by concentration to an oil by vacuum distillation (5−10 mmHg) at 50−55 °C. Dichloromethane (106.5 kg) was added and stirred, and the resulting solution was used immediately in the next step. A sample of the solution was taken; the solvent was removed under vacuum and analyzed to result in a white plastic resinous oil with a calculated 107% yield, 32.8 kg, of **1** and the following characteristics.

^1H NMR (200 MHz, DMSO): δ 12.29 (br s, 1H), 7.00 (d, 1H, J = 8.0 Hz), 3.91 (m, 1H), 1.70−0.71 (m, 13H), 1.36 (s, 9H). $[\alpha]_D$ = −9.1° (c = 1.0, MeOH). HPLC assay: 96.4% by area %, corrected for toluene; Phenomenex (5 μm, 4.6 × 250 mm) C-18 column at 40 °C; mobile phase, 50:50 acetonitrile:0.5 M aqueous triethylamine, pH adjusted to 3.0 with H_3PO_4; flow rate = 1.0 mL/min; UV detector at 214 nm. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 60.89; H, 9.81; N, 4.97.

(*S*)-[1-(1-Cyclohexylmethyl)-2-(methoxymethylamino)-2-oxoethyl]carbamic Acid, 1,1-Dimethylethyl Ester (2). After the dichloromethane solution of **1** (estimated as 100.6 kg/30.6 kg, 112.7 mol) was cooled to about −40 °C, 13.9 kg (140.1 mol) of *N*-methylpiperidine was added slowly, maintaining the batch temperature below −30 °C. Ethyl chloroformate (14.9 kg, 137.3 mol) was added slowly. The reaction mixture was stirred at about −40 °C for about 2 h. A solution of 13.2 kg (135.3 mol)

(14) This did not occur with LiCl. For related interest, see: Hendrix, J. C.; Halverson, K. J.; Jarrett, J. T.; Lanbury, P. T., Jr. *J. Org. Chem.* **1990**, *55*, 4517−4518. Claudy, P.; Bonnetot, B.; Mathurin, D.; Turck, G. *Thermochim. Acta* **1977**, *20*, 315−323.

(15) For related chemistry of carboxylate reactions with toluene and *n*-butyllithium, see: Lochmann, L.; Trekoval, J. *J. Organomet. Chem.* **1987**, *326*, 1−7. Schlosser, M.; Hartmann, J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 508.

of *N*,*O*-dimethylhydroxylamine hydrochloride and 13.9 kg (140.1 mol) of *N*-methylpiperidine in 91 kg of dichloromethane was added slowly to the reaction mixture, maintaining the batch temperature at about −30 °C. The reaction mixture was slowly warmed to about 20 °C and stirred for at least 8 h. Toluene (50 kg) and 35 L of water were added to the reaction mixture, and the layers were separated. The organic layer was washed once with 35 L of water, three times with 1% hydrochloric acid (16 kg), and once with sodium bicarbonate solution (1.9 kg in 30 L of water). The organic layer was concentrated by atmospheric distillation to an oil. Toluene (78 kg) was added, and the solution was concentrated by vacuum distillation to obtain 32.2 kg (90.8% yield) of **2** as a solution in about 55 L of toluene. A sample was taken, and **2** was isolated as a pale brown oil by removing excess solvents under vacuum for analysis.

^{1}H NMR (200 MHz, DMSO): δ 6.87 (d, 1H, J = 8.4 Hz), 4.44 (m, 1H), 3.70 (s, 3H), 3.06 (s, 3H), 1.77−0.83 (m, 13H), 1.35 (s, 9H). $[\alpha]^{25}_D = -10.8°$ (c = 1.0, MeOH). GC assay: 91.6%; DB-5 (30 m) column; flow rate = 1.0 mL/min; injection = 280 °C, FID detection = 300 °C; program set at 50 °C for 2 min, 15 °C/min ramp to 270 °C for 9 min. Anal. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.09; H, 9.89; N, 8.65.

(*S*)-(2-Cyclohexyl-1-formylethyl)carbamic Acid, 1,1-Dimethylethyl Ester (3). A solution of **2** (33.7 kg, 107.2 mol, in 30.7 kg of toluene) was concentrated and charged to a solution of 50.8 kg of sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) in 95 L of toluene at about −15 °C. After the mixture stirred at about −15 °C for about 1.5 h, the reaction was quenched with an aqueous sodium chloride solution (51.3 kg in 286 L of water). The layers were separated, and the organic layer was washed three times with a 5% hydrochloric acid solution (136, 68, and 68 kg), two times with dilute sodium hydroxide solution (1.2 kg of 50% NaOH in 15 L of water), and once with brine (19 kg of NaCl in 54 L of water) and dried over 31 kg of magnesium sulfate. The solution was filtered and partially concentrated under vacuum and the resulting unstable optically active **3** immediately used as a solution. A sample of the aldehyde **3** was isolated as a clear oil by removing excess solvents under vacuum and analyzed immediately.[16]

^{1}H NMR (200 MHz, DMSO): δ 9.41 (s, 1H), 7.20 (m, 1H), 3.87 (m, 1H), 1.75−0.81 (m, 13H), 1.37 (s, 9H). $[\alpha]^{25}_D = -28.2°$ (c = 1.0, MeOH). GC assay: 79%; DB-5 (30 m) column; flow rate = 2.0 mL/min; injection = 280 °C, FID detection = 300 °C; program set at 50 °C for 2 min, 15 °C/min ramp to 270 °C for 9 min.

[*R*-(*R,*S**)]-1-(Cyclohexylmethyl)-2-cyano-2-hydroxycarbamic Acid, 1,1-Dimethylethyl Ester (4).** Potassium cyanide (1.55 g) and tetrabutylammonium iodide (1.83 g) were added to a solution of water (300 mL), acetone cyanohydrin (94.75 g, 1113 mmol), and **3** (188.7 g, 739 mmol, in about 915 mL of heptane, assuming 100% yield of **3**). The reaction mixture was stirred overnight at 25 °C. The two-phase system was washed five times with 300 mL of water. The resulting slurry was filtered, rinsed with heptane, and dried to obtain 190.9 g of **4** as a white crystalline solid (91.5% yield, over two steps).

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.84 (d, 1H), 4.60 (m, 2H), 3.82 (m, 1H), 1.80−0.90 (m, 13H), 1.45 (s, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 156.4, 118.5, 81.1, 65.1, 51.9, 34.1, 33.9, 32.3, 28.3, 27.9, 26.1, 25.9. $[\alpha]_D = -47.16°$ (c = 1.0, methanol). HPLC assay: 97.4% by area %. Supelco DB (5 μm, 4.6 × 250 mm) C-18 column, int = 40 °C, ext = 35 °C; mobile phase, 45:55 acetonitrile:water; flow rate = 1.5 mL/min; RI detector. Anal. Calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28; N, 9.92. Found: C, 64.10; H, 9.55; N, 9.64.

[*R*-(*R,*S**)]-β-Amino-α-hydroxycyclohexanebutanoic Acid, Monohydrochloride (5).** The crystalline solid **4** (177.1 g, 627.1 mmol) and 1.25 L of concentrated aqueous hydrochloric acid were heated at 80 °C for 3 h and cooled to 0 °C. The resulting slurry was filtered and dried to obtain 132.8 g of **5** as a white crystalline solid (89.1% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.20 (d, 1H, J = 3.4 Hz), 3.49 (m, 1H), 1.50−0.69 (m, 13H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 177.5, 72.6, 54.2, 39.6, 36.2, 35.8, 35.4, 29.1, 28.9, 28.7. IR (cm^{-1}): 1728, 1072. $[\alpha]^{25}_D = -13.4°$ (c = 1.08, water). Mp: 210.4−213.1 °C. HPLC assay: 100% by area % (RI), 98.1% by area % (UV); Nucleosil (5 μm, 4.6 × 250 mm) C-18 column at 24 °C; mobile phase, 105:90 methanol:0.5 M aqueous triethylamine, pH adjusted to 2.5 with H_3PO_4; flow rate = 1.0 mL/min; RI detector, UV detector at 210 nm. Anal. Calcd for $C_{10}H_{19}NO_3$·HCl: C, 50.52; H, 8.48; N, 5.89. Found: C, 50.61; H, 8.67; N, 5.78.

[*R*-(*R,*S**)]-β-[(Ethoxycarbonyl)amino]-α-hydroxycyclohexanebutanoic Acid (6).** The hydrochloride salt **5** (10 kg, 42.1 mol) was dissolved in 33.6 L of water and cooled to 5 °C. The pH was adjusted to about 9.5 using 1 N sodium hydroxide (roughly 85 L), maintaining the temperature at about 5 °C. Ethyl chloroformate (5.0 kg, 46.1 mol) was added. The pH of the reaction mixture was maintained at about 9.5 by the addition of more 1 N sodium hydroxide. The reaction mixture was stirred at 5 °C for 2−3 h. The solution was washed once with 90 L of toluene to remove impurities, and hydrochloric acid was added to the water layer, adjusting the pH to about 2.0. The reaction mixture was extracted by washing the reaction mixture two times with 90 L of toluene. The toluene layers were combined and partially concentrated to obtain 10.5 kg of **6** as a colorless to yellow solution (91.3% yield). The solution was carried on into the next step. A sample was isolated by removing excess solvents under vacuum and gave the following physical characteristics.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.51 (d, 1H, J = 9.7 Hz), 4.20−4.00 (m, 2H), 4.15 (q, 2H, J = 6.7 Hz), 1.16 (t, 3H, J = 6.7 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 175.1, 157.1, 72.1, 61.0, 51.1, 39.8, 34.3, 33.7, 32.9, 26.6, 26.5, 14.4. HPLC assay: 97.72% by area %; Nucleosil (5 μm, 4.6 × 250 mm) C-18 column, int = 35 °C, ext = 40 °C; mobile phase, 50:50 acetonitrile:0.01 M aqueous tetrabutylammonium hydrogen sulfate, pH adjusted to 3.0 with H_3PO_4; flow rate = 0.9 mL/min; RI detector. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.10; H, 8.68; N, 4.94.

(2*S*,3*R*)-2-[(Ethoxycarbonyl)amino]-1-cyclohexyl-3-hydroxy-6-methylheptan-4-one (7). Lithium bromide (8.5 kg, 99 mol), a 27% toluene solution of **6** (10.5 kg, 38.4 mol), and 13.5 kg of toluene were combined and stirred under a nitrogen atmosphere. After the batch was cooled to 10 °C, 12.6 kg of THF was added over about 20 min while controlling the temperature at <25 °C. The batch was stirred for 20 min and then cooled to −15 °C. An isobutyllithium solution (22.2% in heptane, 46 kg, 158 mol) was slowly added over 6 h while maintaining the temperature between −15 and −3 °C. The reaction was complete after stirring for 2 h at 5−10 °C. A quench solution of 30 kg of ammonium chloride in 90 L of water was prepared and cooled to 5 °C. The toluene reaction mixture was slowly added to the water solution using vigorous agitation. The temperature of the two-phase system was held at 10 °C during the addition, and the mixture was warmed to 25 °C and stirred for 1 h. After the layers were separated, the organic layer was concentrated under vacuum. Acetonitrile (75 kg) was added and the solution concentrated under vacuum to produce a solution weighing 25.6 kg, containing 10.5 kg of **7** (86.8% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.87 (d, 1H, J = 10.1 Hz), 4.31 (m, 1H), 4.03 (s, 1H), 4.01 (q, 2H, J = 7.1 Hz), 2.53 (m, 2H), 2.17 (m, 1H), 1.90−0.80 (m, 11H), 1.19 (t, 3H, J = 6.9 Hz), 0.93 (d, 6H, J = 6.7 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 210.0, 156.1, 78.5, 60.9, 50.0, 46.6, 40.8, 34.2, 33.5, 33.0, 26.5, 26.2, 26.1, 24.5, 22.5, 22.4, 14.5. $[\alpha]_D = -80.2$ (c = 0.015 g/mL). HPLC assay: 92.7% by wt/wt; Ultrasphere (5 μm, 4.6 × 250 mm) C-18 column, int = 40 °C, ext = 35 °C; mobile phase, 60:40 acetonitrile:0.1 M aqueous tetrabutylammonium hydrogen sulfate, pH adjusted to 3.0 with H_3PO_4; flow rate = 1.5 mL/min; RI detector. Anal. Calcd for $C_{17}H_{31}NO_4$: C, 65.14; H, 9.97; N, 4.47. Found: C, 63.70; H, 9.67; N, 7.37.

[2*S*-(2*R,3*S**,4*R**)]-2-Amino-1-cyclohexyl-6-methyl-3,4-heptanediol (9).** To sodium triacetoxyborohydride (6.8 kg, 32.1 mol) in heptane (16 L) was added **7** (10.2 kg, 32.5 mol) dissolved in acetonitrile (14.7 kg) from the above procedure at 20−28 °C. The reaction mixture was stirred for 4 h at 20−24 °C and cooled to 7 °C, the reaction was quenched with 9% aqueous sodium bicarbonate (60 kg) at 7−15 °C, and the mixture was filtered. The solid intermediate was washed with heptane (25 L) and water (20 L) and vacuum dried to obtain 7.1 kg of **8** (69.2% yield).

(16) The aldehyde **3** could be stored for several days packed in dry ice without a change in optical purity measured by optical rotation.

(17) All of the data collected on **9** were identical with established data reported in the literature.[7]

HPLC assay: 98.1% by area %, Supelco DB (5 μm, 4.6 × 250 mm) C-18 column, int = 40 °C, ext = 35 °C; mobile phase, 45:55 acetonitrile:water; flow rate = 1.5 mL/min; RI detector. Anal. Calcd for $C_{17}H_{33}NO_4$: C, 64.73; H, 10.54; N, 4.44. Found: C, 64.95; H, 10.75; N, 4.43.

To **8** (7.1 kg, 22.5 mol) in 29% aqueous methanol (52 kg) was added 45% aqueous potassium hydroxide (11.2 kg), and the reaction solution was heated at reflux for 16 h. To the reaction solution was added heptane (17 L) at 15 °C, and the mixture was reheated to reflux. The solution was cooled to 12−20 °C and the resultant solid collected. The solid product was washed with 17% aqueous methanol (14 kg) and water (20 L) and vacuum dried to obtain 5.1 kg of the off-white crystalline solid **9** (93.1% yield).[17]

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.77 (dt, 1H, J = 9.5, 3.6 Hz), 3.23 (dd, 1H, J = 2.2, 3.6 Hz), 3.04 (dt, 1H, J = 2.1, 6.7 Hz), 1.70−0.80 (m, 16H), 0.96 (d, 3H, J = 6.6 Hz), 0.92 (3H, J = 6.5 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 74.5, 73.3, 48.4, 43.7, 43.3, 34.1, 33.8, 32.9, 26.5, 26.3, 26.1, 24.8, 23.5, 22.0. $[\alpha]^{25}_D = -34.5°$ (c = 1.0, methanol). HPLC assay: 99.49% by wt/wt; Supelco DB (5 μm, 4.6 × 250 mm) C-18 column, int = 40 °C, ext = 35 °C; mobile phase, 35:65 acetonitrile:0.01 M aqueous 1-octanesulfonic acid, sodium salt, 2 mL of triethylamine/L of water, pH adjusted to 3.0 with H_3PO_4; flow rate = 1.5 mL/min; RI detector. Chiral HPLC purity assay: 100%, no enantiomer detected; Beckman ODS (5 μm, 4.6 × 250 mm) C-18 column; mobile phase, 50:50 acetonitrile:water; flow rate = 1.5 mL/min; UV detector at 214 nm.

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